DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Christopher J. Stotka, PharmD
Director, US Regulatory Affairs
GlaxoSmithKline
5 Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

RE: NDA #21-926
Treximet™ (sumatriptan and naproxen sodium) Tablets
MACMIS #17263

Dear Dr. Stotka:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed five online banners (TMC018R0) for Treximet™ (sumatriptan and naproxen sodium) Tablets (TREXIMET) submitted by GlaxoSmithKline (GSK) under cover of Form FDA-2253. The online banners are misleading because they minimize serious risks and inadequately communicate facts material to the presentation about the drug. Thus, the banners misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & (n), 321(n), and FDA implementing regulations. *See* 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i) & (e)(7)(viii).

Background

According to the FDA-approved product labeling (PI), TREXIMET is approved for the following indication:

> TREXIMET is indicated for the acute treatment of migraine attacks with or without aura in adults. Carefully consider the potential benefits and risks of TREXIMET and other treatment options when deciding to use TREXIMET.
>
> TREXIMET is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine . . . Safety and effectiveness of TREXIMET have not been established for cluster headache.

TREXIMET is associated with serious risks. The PI for TREXIMET includes a BOXED WARNING that states (emphasis original):

WARNINGS
Cardiovascular Risk: TREXIMET may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. . . .

Gastrointestinal Risk: TREXIMET contains a nonsteroidal anti-inflammatory drug (NSAID). NSAID-containing products cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. . . .

Additionally, the PI contains numerous other risks associated with the use of TREXIMET. There are contraindications including cardiac, cerebrovascular, or peripheral vascular disease (including the use in patients who have had or are undergoing coronary artery bypass graft (CABG) surgery); uncontrolled hypertension; Monoamine Oxidase-A Inhibitors; hepatic impairment; allergy to naproxen or asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs; and hypersensitivity to sumatriptan. There are also warnings including cardiovascular effects; Serotonin Syndrome; advanced renal disease; anaphylactic/anaphylactoid reactions; potentially fatal skin reactions; and pregnancy.

Minimization of Risk

The banners fail to communicate the serious risks associated with Treximet with a prominence and readability reasonably comparable with the presentation of information related to effectiveness. Specifically, these banners, although varying in exact dimensions, present efficacy claims prominently, utilizing techniques that are designed to emphasize this information, but relegate the presentation of risk information to a small, scrolling portion of the banner that is likely to be ignored by consumers.

The following text claims appear in sequence in the online banners:

- "My migraines are so excruciating."
- "I just want to take my head off."
- "Now from the makers of Imitrex® comes new Treximet™ sumatriptan/ naproxen sodium"
- "Prescription Treximet™ is for acute treatment of migraine attacks in adults."
- "Treximet™ is superior at relieving migraine pain to the active ingredient in Imitrex."
- "Ask your doctor if New Treximet™ sumatriptan/ naproxen sodium is right for you."

As this text appears, a sequence of images is shown on the screen, including: a woman with hands placed on her temples, in discomfort; the same woman, holding her head, which has

been detached from her body; a TREXIMET tablet and a blue dashed-line graphic, and the same woman, head re-attached and smiling.

The information related to effectiveness takes up most of the height of each banner, and these visual presentations are colorful and compelling. For example, the banners begin with a close-up image of eyes squinting in pain, followed by a picture of a headless woman holding her head at her waist, followed by a smiling woman. The image of the headless woman is particularly attention-grabbing. The large font size of the claims and the content of the text also contribute to the prominence of these presentations. The short efficacy claims are thus capable of being easily read in the time they are presented on the screen and are presented in a large, readable font-size, accompanied by striking visual support and messages designed to capture the attention, such as "I just want to take my head off." In addition, the TREXIMET logo is clearly and largely displayed on all screens of the banners.

In striking contrast, the presentation of risk information in the banners uses none of these supporting approaches and is difficult to find and read. As the banners sequence through the efficacy claims, the risk information automatically scrolls in a small slice of the banner. The text in the risk section is small and is formatted in single-spaced block paragraphs, making it difficult to read, and the information scrolls at a predefined speed. This automatic scrolling and the density of the risk information make the presentation almost impossible to read and comprehend in the time allotted. Unlike the efficacy claims in the banners, the risk information is presented without any signals or other attention-grabbing devices to alert readers that this is important information about the drug.

The overall effect of this presentation is to obfuscate the communication of important risk information, misleadingly suggesting that TREXIMET is safer than has been demonstrated by substantial evidence or clinical experience.

Misleading Presentation

The banners include the prominent claim, "Treximet™ is superior at relieving migraine pain to the active ingredient in Imitrex." While it is true that Treximet is superior at relieving sustained migraine pain to the active ingredient in Imitrex, the banners misleadingly fail to appropriately convey the most material information related to this claim, namely, that TREXIMET is a combination of the active ingredient in Imitrex and naproxen sodium. The screen shown before this superiority claim in the banners does include a small disclaimer statement that "TREXIMET is a combination of IMITREX (sumatriptan) and prescription-strength naproxen sodium (an NSAID)," but this statement does not effectively convey the pertinent information. It appears in small font at the bottom of the screen while information about the drug's indication is simultaneously presented and it appears on the screen for just a few seconds. This critical information is not presented in a manner that allows consumers to read, process, and comprehend it.

Conclusion and Requested Action

For the above reasons, the online banners misbrand TREXIMET in violation of the Federal Food, Drug, and Cosmetic Act and implementing regulations. *See* 21 U.S.C. 352(a) & (n); 321(n); 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i) & (e)(7)(viii).

DDMAC requests that GSK immediately cease the dissemination of violative promotional materials for TREXIMET such as those described above. Please submit a written response to this letter on or before March 23, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for TREXIMET as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 17263 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for TREXIMET comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Sharon M. Watson, PharmD
LCDR, USPHS
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Watson
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